REMARKS

The Claimed Invention

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115 and 117-119 are pending in this application.

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115, 118 and 119 define methods of treatment using *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea (Sorafenib), the tosylate salt form for which the drug Nexavar®, and *N*-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(carbamoyl)-4-pyridyloxy) phenyl) urea, a derivative of Sorafenib.

As indicated in the previous response, Claim 117 defines a method for inhibiting raf-kinase in a human or mammal by administering one of these two compounds to a human or other mammal in need thereof. It does not require the treatment of a disease such as cancer in a human or other mammal. It only requires that the inhibition of raf kinase within the human or other mammal be inhibited. Such activity is clearly enabled by the assays in the disclosure.

Claims to treating carcinoma of the colon

Applicants acknowledge that claims 104, 115, 118 and 119 directed to treating carcinoma of the colon have been found to satisfy 35 USC §112, first paragraph. Given the scope of the disclosure provided, including the enabling disclosure for treating carcinoma of the colon, it would at most involve routine experimentation, if any at all, for one of ordinary skill in the art to treat other solid tumors with one of the two compounds named. Explicitly providing dedicated assays for each form of cancer is not necessary to enable the methods claimed. See, for example, *In re Howarth,* 654 F.2d 105, 210 U.S.P.Q. 689 (CCPA 1981) ("An inventor need not … explain every detail since he is speaking to those skilled in the art.)

Rejection under 35 U.S.C. §112, first paragraph

Claims 74, 81, 87, 93, 100-103, 106-108, 110-114 and 117 stand rejected under 35 U.S.C. §112, first paragraph.

The examiner has yet to provide any direct evidence that one skilled in the art would not find the claimed subject matter enabled by the specification. Since the last response, the drug Nexavar has been approved in more countries and has been enrolled in more clinical trials. The number of clinical trails reported on www.clinicaltrials.gov employing Nexavar is now 326. As indicated in the last response, Nexavar® has been studied in more than 20 tumor types and in nearly 8000 clinical trial patients. www.medicalnewstoday.com/articles/42734.php, including lung, thyroid, gastric and ovarian cancers, as shown by the publications made of record earlier and discussed below. In the previous response Applicants cited specific studies on multiple cancers by Awada et al., Br J Cancer. 2005 May 23;92(10):1855-61, Clark et al, Clinical Cancer Res.2005 Aug 1,11(15):5472-80, Moore et al., Ann Oncol. 2005 Oct; 16 (10):1688-94.Epub 2005 Jul 8, Escudier et al, N Engl J Med 2007 Jan 11, 356 (2):125-34.

This 320 clinical studies including those of Awada et al, Clark et al, Moore et al., and Escudier et al, 1) demonstrate it does not require undue experimentation to practice the claimed methods from applicants disclosure and 2) demonstrate there is correlation between the models disclosed in the application and efficacy in contrast to the studies by Johnson et al. cited by the examiner.

The approved use of Nexavar and the methods employed in the studies above are consistent with the teachings of the disclosure of this invention. No evidence has been presented that any researcher needed to significantly deviate from the teachings within this application to use Nexavar or that the assays disclosed were ineffective in identifying active compounds.

These clinical studies endorse the teachings in the specification and demonstrate the claimed methods are enabled by the specification. The dosages, modes of administration and patient classes used in these studies are consistent with the teachings in this specification. No evidence has been presented to question the teachings within the specification to support the rejection.

Applicants rely on the state of the art references (Monia, Kolch, Daum et al. and Fridman et al) to show the correlation between the inhibition of raf kinase with the inhibition of the growth of a variety of solid tumor types (Monia et al.), the blocking cell proliferation (Kolch et al.) and the reversion of transformed cells to the normal growth phenotype (Daum et al., Fridman et al).

Applicants do not rely on Awada et al, Clark et al, Moore et al., and Escudier et al, to show the state of the art and need not do so since the disclosure is clearly enabling for the methods claimed. Applicants need not provide any references to show the claimed uses were conventional.

The disclosure in the specification provides the details necessary to establish therapeutic treatments with the compounds disclosed therein. The adequacy of this disclosure is confirmed by the studies discusses above and others made of record in the IDS filed on June 29 2007.

The Examiner maintains "There is no evidence of record that the claimed compounds are actually efficacious in treating all types of solid tumor, carcinoma, myeloid disorders or adenoma or inhibit RAF–kinase generally." This is clearly not true in view of the numerous studies made of record. The drug Nexavar has been administered in thousands of patients and efficacy has been confirmed in that Nexavar has been approved for the treatment of renal cell carcinoma (RCC) in more than 70 countries and hepatocellular carcinoma (HCC) in more than 40 countries. Nexavar was the first drug approved for use in treating renal cell carcinoma (RCC), such that the drugs efficacious properties are not only real, they are unique. As mentioned above, it is reported that over 320 clinical trials are using Nexavar.

Clinical trials such as these were not performed at the time of filing but such evidence of efficacy is not necessary to satisfy the requirements of the statute. An applicant is not required to perform the claimed methods in clinical trials to satisfy the statute. With regard to the requirement of utility, the Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995), stated that:

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

If such testing is not required to show utility it also should not be required to show enablement based on the same principles.

There is no requirement that an applicant provide any working examples. See, for example, *Marzocchi*, supra, stating that how "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

There is clearly no requirement that Applicants provide working examples relating to the treatment of every claimed disease to satisfy the statute. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (Fed. Cir. 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses).

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to perform the methods claimed. Instead of relying on probative evidence, the rejection is improperly based on bare allegations and conclusions. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the use of the claimed compounds without undue experimentation.

Applicants maintain that the express disclosure within the specification is sufficient to enable all of the claims herein and that further assays or data to support the methods of treatment are not necessary. Based on the teachings within the art of the broad spectrum of activity of raf kinase inhibitors, one skilled in the art would recognize that the compounds recited in the claims herein having raf kinase activity would be effective in treating the diseases claimed.

Claims 87, 93, 100-103,108, 109 and 111-114

The specification expressly teaches the compounds disclosed are suitable for the treatment of the cancers named in claims 87, 93, 100-103,108, 109 and 111-114,(lung, pancreas, thyroid, bladder and myeloid leukemia). There is no reason to doubt the general and specific disclosures therein regarding the treatment of solid tumors such as these. In addition, studies of record have confirmed the compound

Nexavar is efficacious in treating colon cancer (Awada et al, Clark et al, Moore et al), lung cancer (Awada et al.), pancreatic cancer (Clark et al and Moore et al.) and myeloid leukemia (Éclair, et al., "96th Annual Meeting, Anaheim/Orange County, CA, April 16-20, 2005).

In the view of the lack of evidence to support the allegation that these claims are not enabled, the methods of Claims 87, 93, 100-103,108, 109 and 111-114 are clearly enabled by the specification and the rejection of these claims under 35 USC §112 first paragraph, should be withdrawn.

Claim 117

Claim 117 is directed to a method of inhibiting raf -kinase in a human or other mammal with one of the two compounds listed. No reasons have been given for rejecting this claim as not enabled. It is not a method of treatment claim for any condition, including cancer, so the issues raised by the examiner regarding the complexities in treating cancer are moot.

The specification provides sufficient guidance to prepare the two urea compounds and also provides sufficient guidance on how to prepare and administer compositions with these compounds, including dosages. The specification also shows that the free base of these compounds, compounds 42 and 43, inhibit raf kinase in the assays disclosed.

The examiner has not identified any element of the claim for which the disclosure is allegedly deficient and has not identified any claim term, which is allegedly indefinite. Instead, the examiner reads limitations into the claim regarding the treatment of diseases. There is no basis for incorporating treatment limitations into the claim, which is improper, (*See Phillips v. AWH Corp.,* 415 F.3d 1303, 1313, 75 USPQ2d 1321, 1326 (Fed. Cir. 2005) (en banc), MPEP 2111.01, and *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)).

In that there is no basis for referring to the specification for the meaning of any claim term and there clearly is no basis for reading treatment limitations into the claim, the rejection of claim 117 should be withdrawn.

For the reasons indicated above, Applicants maintain that they have provided more than adequate guidance and examples to enable the claimed invention and

submit all claims meet the requirements of 35 U.S.C. §112, first and second paragraphs.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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